WE CLAIM:

1. A method for selecting ligands that have an affinity for a target molecule that is equal to or greater than a baseline affinity comprising:

selecting a mass spectrometer;

selecting a standard ligand that forms a non-covalent binding complex with said target molecule;

mixing an amount of said standard ligand with an excess amount of said target molecule such that unbound target molecule is present in said mixture;

introducing said mixture of said standard ligand and said target molecule into said mass spectrometer;

adjusting the operating performance conditions of said mass spectrometer such that the signal strength of said standard ligand bound to said target molecule is from 1% to about 30% of the signal strength of unbound target molecule;

introducing at least one further ligand into a test mixture of said target molecule and said standard ligand;

introducing said test mixture into said mass spectrometer;

identifying any complexes of said further ligand and said target wherein said ligand has greater than said baseline affinity for said target molecule by discerning those signals that have a signal strength greater than the background noise of said mass spectrometer.

2. The method of claim 1 wherein said mass spectrometer is an electrospray mass spectrometer.

3. The method of claim 1 wherein said target molecule is a RNA, a protein, a RNA-DNA duplex, a DNA duplex, a polysaccharide, a phospholipid or a glycolipid.

4. The method of claim 1 wherein said target molecule is RNA.

5. The method of claim 1 wherein said target molecule is RNA and said baseline affinity expressed as a dissociation constant is about 50 millimolar.

6. The method of claim 1 wherein said target molecule is RNA and said standard ligand is ammonium, a primary amine, a secondary amine, a tertiary amine, an amino acid or a nitrogen containing heterocycle.

7. The method of claim 1 wherein said target molecule is RNA and said standard ligand is ammonium.

8. The method of claim 1 wherein said target molecule is a protein and said standard ligand is an ester, a phosphate, a borate, an amino acid or a nitrogen containing heterocycle.

9. The method of claim 2 wherein said electrospray mass spectrometer includes a desolvation capillary or countercurrent gas and a lens element; and

said adjustment of said operating performance conditions includes adjustment of said voltage potential across said capillary and said lens element.

10. The method of claim 9 wherein said adjustment of said operating performance conditions further includes adjustment of source voltage potential to give a stable electrospray ionization as monitored by the ion abundance of free target molecule.

11. The method of claim 9 wherein said adjustment of

said operating performance conditions further includes adjustment of the temperature of the desolvation capillary or **countercurrent heating gas.**

12. The method of claim 9 wherein said adjustment of said operating performance conditions further includes adjustment of the operating gas pressure within said mass spectrometer downstream of said desolvation capillary.

13. The method of claim 9 wherein said target molecule is RNA and said standard ligand is ammonium ion; and

said adjustment of said voltage potential across said capillary and said lens element generates an abundance of an ion from a monoammonium-RNA complex to from about 10% to about 20% of the abundance of the ion from target RNA.

14. The method of claim 4 said RNA molecule is from about 10 to about 200 nucleotides in length.

15. The method of claim 4 wherein said RNA molecule is from about 15 to about 100 nucleotides in length.

16. The method of claim 4 wherein said RNA molecule comprises an isolated or purified portion of a larger RNA molecule.

17. The method of claim 4 wherein said RNA has secondary and ternary structure.

18. The method of claim 2 further including selecting said electrospray mass spectrometer as a mass spectrometer having a gated ion storage devices for effecting thermolysis of said test mixture in said mass

spectrometer.

19. The method of claim 2 wherein said mass spectrometer includes mass analysis by quadrupole, quadrupole ion trap, time-of-flight, FT-ICR or hybrid mass detectors.

20. The method of claim 2 wherein said electrospray mass spectrometer includes Z-spray, microspray, off-axis spray or pneumatically assisted electrospray ionization.

21. The method of claim 20 wherein said Z-spray, microspray, off-axis spray or pneumatically assisted electrospray ionization each further include countercurrent drying gas.

22. The method of claim 1 further including storing the relative abundance and stoichiometry of said complexes of said ligand and target in a relational database that is cross-indexed to the structure of said ligand.

23. The method of claim 1 wherein said further ligand is a member of a set of ligands.

24. The method of claim 23 wherein each of the members of said set of ligands, independently, has a molecular mass less than about 1000 Daltons and has fewer than 15 rotatable bonds

25. The method of claim 23 wherein each of the members of said set of ligands, independently, has a molecular mass less than about 600 Daltons and has fewer than 8 rotatable bonds.

26. The method of claim 23 wherein each of the members of said set of ligands, independently, has a molecular

mass less than about 200 Daltons, has fewer than 4 rotatable bonds or no more than one sulfur, phosphorous or halogen atom.

27. The method of claim 1 wherein said signal strength is measured by the relative ion abundance.

28. The method of claim 1 including a plurality of target molecules.

29. The method of claim 28 including a plurality of standard ligands.

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30. A method of selecting those members of group of compounds that can form a non-covalent complex with a target molecule and where the affinity of the members for the target molecule is greater than a baseline affinity comprising:

selecting a mass spectrometer;

selecting a standard compound that forms a non-covalent binding complex with said target molecule;

mixing an amount of said standard compound with an excess amount of said target molecule such that unbound target molecule is present in said mixture;

introducing said mixture of said standard compound and said target molecule into said mass spectrometer;

adjusting the operating performance conditions of said mass spectrometer such that the signal strength of said standard compound bound to said target molecule is from 1% to about 30% of signal strength of unbound target molecule;

introducing a sub-set of said group of compounds into a test mixture of said target molecule and said standard compound;

introducing said test mixture into said mass

spectrometer;

identifying the members of said sub-set that form complexes with said target with an affinity *greater* than said baseline by discerning those signals that have a signal strength greater than the background noise of said mass spectrometer and identifying the member by their respective molecular mass.

31. The method of claim 30 wherein said signal is measured as the relative ion abundance.

32. The method of claim 30 wherein said sub-set comprises from about 2 to about 8 member compounds.

33. The method of claim 30 wherein said group of compounds comprises a collection library of diverse compounds.

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34. The method of claim 33 wherein said collection library of diverse compounds comprises a historical repository of compounds, a collection of natural products, a collection of drug substances, a collections of intermediates produced in forming drug substances, a collection of dye stuffs, a commercial collection of chemical substances or a combinatorial library of related compounds.

35. The method of claim 33 wherein collection library of diverse compounds comprises a library of compounds having from 2 to about 100,000 members.

36. The method of claim 30 further including storing the relative abundance and stoichiometry of said complexes of said member compounds and said target in a relational database.

37. The method of claim 36 further including cross-indexing said relative abundance and stoichiometry of said completes to the structures of said member compounds.

38. The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 1000 Daltons and has fewer than 15 rotatable bonds.

39 The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 600 Daltons and has fewer than 8 rotatable bonds.

SUB A4

40. The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 200 Daltons, has fewer than 4 rotatable bonds or no more than one sulfur, phosphorous or halogen atom.

41. The method of claim 30 wherein said mass spectrometer is an electrospray mass spectrometer.

42. The method of claim 30 wherein said target molecule is a RNA, a protein, a RNA-DNA duplex, a DNA duplex, a polysaccharide, a phospholipid or a glycolipid.

43. The method of claim 30 wherein said target molecule is RNA.

SUB A5

44. The method of claim 30 wherein said target molecule is RNA and said preset baseline affinity expressed as a dissociation constant is about 50 millimolar.

45. The method of claim 30 wherein said target molecule is RNA and said standard ligand is ammonium.

46. The method of claim 30 wherein said electrospray mass spectrometer includes a desolvation capillary and a lens element; and

said adjustment of said operating performance conditions includes adjustment of the voltage across said capillary and said lens element.

47. A method of detecting small molecule-RNA complexes having an affinity as expressed as a dissociation constant of from about nanomolar to about 100 millimolar comprising:

selecting an electrospray mass spectrometer;

selecting a standard compound that forms a non-covalent binding complex with said RNA at an affinity of about 50 millimolar as measured as a dissociation constant;

mixing an amount of said standard compound with an excess amount of said RNA such that unbound RNA is present in said mixture;

introducing said mixture of said standard compound and said target molecule into said mass spectrometer;

adjusting the operating performance conditions of said mass spectrometer such that the relative ion abundance of said standard compound bound to said RNA is from 1% to about 30% of the relative ion abundance of unbound RNA;

introducing a set of small molecular compounds into a test mixture of said RNA and said standard compound;

introducing said test mixture into said mass spectrometer;

identifying the members of said set of compounds

that form complexes with said RNA by discerning those signals that have a relative ion abundance greater than the baseline noise of said mass spectrometer; and

identifying the members by their respective molecular masses.

48. The method of claim 47 further including storing the relative abundance and stoichiometry of said complexes of said member compounds and said RNA in a relational database.

49. The method of claim 48 further including cross-indexing said relative abundance and stoichiometry of said completes to the structures of said member compounds.

50. The method of claim 47 wherein each of said small molecular compounds, independently, has a molecular mass less than about 200 Daltons.

51. The method of claim 47 wherein each of said small molecular compounds, independently, has fewer than 4 rotatable bonds.

52. The method of claim 47 wherein each of said small molecular compounds, independently, has no more than one sulfur, no more than one phosphorous or no more than one halogen atom.

53. A method of detecting small molecule-RNA complexes having from about nanomolar to about 100 millimolar affinity as measured as a dissociation constant comprising:

selecting an electrospray mass spectrometer;

mixing an amount of an ionic ammonium compound with

an excess amount of said RNA such that unbound RNA is present in said mixture;

introducing said mixture of said ammonium compound and said target molecule into said mass spectrometer;

adjusting the operating performance conditions of said mass spectrometer such that the relative ion abundance of ammonium ion bound to said RNA is from 1% to about 30% of the relative ion abundance of unbound RNA;

introducing a set of small molecular compounds into a test mixture of said RNA and said ammonium compound;

introducing said test mixture into said mass spectrometer;

identifying the members of said set of compounds that form complexes with said RNA by discerning those signals that have a relative ion abundance greater than the base line signal of said mass spectrometer; and

identifying the members by their respective molecular masses.

54. The method of claim 53 wherein each of said small molecular compounds, independently, has a molecular mass less than about 200 molecular mass units.

55. The method of claim 53 wherein each of said small molecular compounds, independently, has fewer than 4 rotatable bonds.

56. The method of claim 53 wherein each of said small molecular compounds, independently, has no more than one sulfur, no more than one phosphorous or no more than one halogen atom.

57. A method for determining the relative interaction between at least two ligands with respect to a target substrate comprising:

mixing an amount of each of said ligands with an amount of said target substrate to form a mixture;

analyzing said mixture by mass spectrometry to determine the presence or absence of a ternary complex corresponding to simultaneous adduction of two of said ligands with said target substrate;

wherein the absence of said ternary complex indicates that binding of said ligands to said target substrate is competitive and the presence of said ternary complex indicates that binding of said ligands to said target substrate is other than competitive.

58. The method of claim 57, further comprising:

determining from said mass spectrometry analysis of the mixture, the ion abundance of i) said ternary complex, ii) a first binary complex corresponding to the adduction of a first of said ligands with the target substrate, iii) a second binary complex corresponding to the adduction of a second of said ligands with said target substrate, and iv) said target substrate unbound by either first or second ligand;

calculating the relative ion abundance of the contributing binary complexes corresponding to the relative ion abundance of the first binary complex with respect to the unbound target substrate multiplied by the absolute ion abundance of the second binary complex and the relative ion abundance of the second binary complex with respect to the unbound target substrate multiplied by the absolute ion abundance of the first binary complex; and

comparing the absolute ion abundance of said ternary complex with respect to said unbound target substrate, to the sum of the relative ion abundances of the contributing binary complexes;

wherein an equal ion abundance of said ternary

complex compared to the sum of the relative ion abundances of the contributing binary complexes indicates a concurrent binding interaction of the ligands to the target substrate, a greater ion abundance of said ternary complex indicates a cooperative binding interaction of the ligands to the target substrate, and a lesser ion abundance of said ternary complex indicates a competitive binding interaction of the ligands to the target substrate.

59. The method of claim 57, wherein said ligands are present in said mixture in molar excess to said target substrate.

60. The method of claim 59, wherein said target substrate is not saturated with said ligands.

61. A method of determining binding interaction between a first ligand and a second ligand with respect to a target substrate comprising:

exposing said target substrate to said first and second ligands to form a mixture comprising i) a ternary complex (TL1L2) of said ligands bound to the target substrate, ii) a first binary complex (TL1) of said first ligand and said target substrate; iii) a second binary complex (TL2) of said second ligand and said target substrate and iv) target substrate (T) unbound by either first or second ligand;

analyzing said mixture by mass spectrometry to determine the absolute ion abundance of said ternary complex (TL1L2), said first binary complex (TL1), said second binary complex (TL2) and said target substrate (T) unbound to said first or second ligands; and

comparing the ion abundance of said first and second binary complexes TL1 and TL2, said ternary complex TL1L2

and said target substrate (T) in any of the following formulae:

$$y = TL1L2 - TL1 \times \frac{TL2}{T} - TL2 \times \frac{TL1}{T}$$

or

$$y = TL1L2 - 2 \times \frac{TL1 \times TL2}{T}$$

whereby a value for y equal to zero indicates that the first and second ligand have a concurrent binding interaction for the target substrate; a value greater than zero indicates that the first and second ligand have a cooperative binding interaction for the target substrate; and a value less than zero indicates that the first and second ligand have a competitive binding interaction for the target substrate.

62. The method according to claim 61, wherein a greater ion abundance of said first binary complex (TL1) than said second binary complex (TL2) in the mixture indicates that said first ligand has greater affinity for the target substrate than the second ligand.

63. The method according to claim 57, wherein the absence of said ternary complex in said mixture indicates that the first and second ligands bind to said target substrate at the same location and the presence of said ternary complex indicates that the first and second ligands bind to said target substrate at distinct location.

64. A method of determining the relative proximity of

binding sites for a first ligand and a second ligand on a target substrate comprising:

exposing said target substrate to a mixture of the second ligand and a plurality of derivative compounds of the first ligand, said first ligand derivatives comprising the chemical structure of the first ligand and at least one substituent group pending therefrom;

analyzing said mixture by mass spectrometry to identify a first ligand derivative which inhibits the binding of said second ligand to the target substrate or has a competitive binding interaction with the second ligand for the target substrate.

65. The method according to claim 63, wherein substituent groups on the first ligand binding derivatives are iteratively lengthened to determine the relative proximity of the second ligand binding site.

66. A method of determining the relative orientation of a first ligand to a second ligand when bound to a target substrate comprising:

exposing said target substrate to a mixture of the second ligand and a plurality of derivative compounds of the first ligand, said first ligand derivatives comprising the chemical structure of the first ligand and having a substituent group pending therefrom;

analyzing said mixture by mass spectrometry to identify a first ligand derivative which inhibits the binding of said second ligand to the target substrate or has a competitive binding interaction with the second ligand for the target substrate.

67. The method according to claim 66, wherein the relative orientation of the first and second ligands when bound to said target substrate is relative to the

position at which said substituent is attached to the chemical structure of the first ligand.

68. The method according to claim 67, wherein the substituent group is iteratively attached to different locations on the first ligand derivatives to determine the relative orientation of the first ligand binding site to the second ligand binding site.

69. A screening method for determining compounds having binding affinity to a target substrate comprising:

identifying by mass spectrometry in a mixture comprising said ligands and target substrate a first and second ligand that bind to said target substrate non-competitively; and

concatenating said first and second ligands to form a third ligand having greater binding affinity for the target substrate than either first or second ligand.

70. The method of claim 69, wherein the relative proximity of said first and second ligand binding sites is determined by:

exposing said target substrate to a mixture of the second ligand and a plurality of derivative compounds of the first ligand, said first ligand derivatives comprising the chemical structure of the first ligand and at least one substituent group pending therefrom;

analyzing said mixture by mass spectrometry to identify a first ligand derivative which inhibits the binding of said second ligand to the target substrate or has a competitive binding interaction with the second ligand for the target substrate.

71. The method of claim 69, wherein the relative orientation of said first and second ligands when bound

to said target substrate is determined by:

exposing said target substrate to a mixture of the second ligand and a plurality of derivative compounds of the first ligand, said first ligand derivatives comprising the chemical structure of the first ligand and having a substituent group pending therefrom;

analyzing said mixture by mass spectrometry to identify a first ligand derivative which inhibits the binding of said second ligand to the target substrate or has a competitive binding interaction with the second ligand for the target substrate.

72. The method of claim 71, wherein said substituent group is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, acyl, acyloxy, aryl, aralkyl, hydroxyl, hydroxylamino, keto (=O), amino, alkylamino, mercapto, thioalkyl, halogen, nitro, haloalkyl, phosphorous, phosphate, sulfur and sulfate.

73. The method of claim 69, wherein the relative proximity of said first and second ligand binding sites is determined by *in silico* calculation.

74. The method of claim 69, wherein the relative orientation of said first and second ligands when bound to said target substrate is determined by *in silico* calculation.

75. The method of claim 69, wherein the relative proximity of said first and second ligand binding sites is determined by NMR.

76. The method of claim 69, wherein the relative orientation of said first and second ligands when bound

to said target substrate is determined by NMR.

77. The method of claim 69, wherein said third ligand comprises the chemical structures of the first and second ligands covalently linked by a linking group having a length and points of attachment to the ligands corresponding to the relative proximity and orientation of said substituent group.

78. The method of claim 77, wherein said linking group is selected from a bond, alkylene, alkenylene, alkynylene, arylene, ether, alkylene-esters, thioether, alkylene-thioesters, aminoalkylene, amine, thioalkylene and heterocycles.

79. A method for modulating the binding affinity of ligands for a target molecule comprising:

selecting a first ligand fragment;

selecting a second ligand fragment;

exposing said target molecule to said first and said second ligand fragments;

interrogating said target molecule exposed to said ligand fragments in a mass spectrometer to identify binding of said ligand fragments to said target molecules; and

concatenating said ligand fragments together in a structural configuration that improves the binding properties of said fragments for said target molecule.

80. The method of claim 79 wherein said improvement in binding properties comprises an increase in binding affinity or a conformational change induced in said target molecule.

81. The method of claim 79 wherein said improvement in binding properties comprises an increase in binding affinity.

82. The method of claim 79 wherein said improvement in binding properties comprises a conformational change induced in said target molecule.

83. The method of claim 79 comprising:

modifying said first ligand fragment by making a structural derivative of said ligand fragment to form a modified first ligand fragment;

re-exposing said target molecule to said modified first ligand fragment and said second ligand fragment;

re-interrogating said target molecule exposed to said modified first ligand fragment and said second ligand fragment in said mass spectrometer to identify binding of the modified first ligand fragment and said second ligand to said target molecules; and

concatenating said modified first ligand fragment and said second ligand fragment together in a structural configuration that increases the binding affinity to said target molecule.

84. The method of claim 83 comprising:

choosing said second ligand fragment;

modifying said second ligand fragment by making a structural derivative of said second ligand fragment to form a modified second ligand fragment;

re-exposing said target molecule to said modified first ligand fragment and said modified second ligand;

re-interrogating said target molecule exposed to said modified first ligand fragment and said modified second ligand fragment in said mass spectrometer to identify binding of modified ligand fragments to said

target molecules; and

covalently joining said modified first ligand fragment and said modified second ligand fragment together in a structural configuration that mimics said conformation or location of said fragments on said target molecule.

85. The method of claim 83 wherein said first ligand fragment is modified by replacing one atom or one substituent group on said ligand with a different atom or a different substituent group.

86. The method of claim 85 wherein said first ligand fragment is modified by replacing a hydrogen atom with a substituent group.

87. The method of claim 86 wherein said substituent group is alkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, acyl, acyloxy, aryl, aralkyl, hydroxyl, hydroxylamino, keto (=O), amino, alkylamino, mercapto, thioalkyl, halogen, nitro, haloalkyl, phosphorous, phosphate, sulfur or sulfate.

88. The method of claim 86 wherein said first ligand fragment is selected as a ligand containing a ring and said first ligand fragment is modified by expanding or contracting the size of said ring.

89. The method of claim 83 wherein said second ligand fragment is modified by replacing one atom or substituent group on said ligand with a different atom or different substituent group.

90. The method of claim 89 wherein said second ligand fragment is modified by replacing a hydrogen atom with a

substituent group.

91. The method of claim 90 wherein said substituent group is alkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, acyl, acyloxy, aryl, aralkyl, hydroxyl, hydroxylamino, keto (=O), amino, alkylamino, mercapto, thioalkyl, halogen, nitro, haloalkyl, phosphorous, phosphate, sulfur or sulfate.

92. The method of claim 89 wherein said second ligand fragment is selected as a ligand containing a ring and said ligand fragment is modified by expanding or contracting the size of said ring.

93. The method of claim 79 further including refining said binding of said ligand fragment to said target molecule using molecular modeling.

94. The method of claim 93 wherein said refining comprises:

virtually concatenating said ligand fragments together to form an *in silico* 3D model of said concatenated ligand fragments;

positioning said *in silico* 3D model of said concatenated ligand fragments on an *in silico* 3D model of said target molecule;

scoring said positioning of said *in silico* 3D model of said concatenated ligand fragments on said *in silico* 3D model of said target molecule; and

refining said positioning of said *in silico* 3D model of said concatenated ligand fragments on said *in silico* 3D model of said target molecule using the results of said scoring.

95. The method of claim 94 wherein said scoring uses one or more hydrophobic, hydrogen-bonding and electrostatic interactions between said *in silico* 3D model of said concatenated ligand fragments and said *in silico* 3D model of said target molecule.

96. The method of claim 94 further including;

covalently joining said ligand fragments together in a structural configuration that mimics said virtually concatenating said ligand fragments;

re-exposing said target molecular to said covalently joined ligand fragments; and

re-interrogating said target molecule exposed to said covalently joined ligand fragments in said mass spectrometer to identify binding of said covalently joined ligand fragments and said target molecule.

97. The method of claim 79 wherein said binding is competitive, concurrent or cooperative binding.

98. The method of claim 97 wherein ligand fragments exhibiting one of cooperative or concurrent binding with said target molecule are selected for concatenation.

99. The method of claim 97 wherein ligand fragments exhibiting cooperative binding with said target molecule are selected for concatenation.

100. The method of claim 97 wherein ligand fragments exhibiting concurrent binding with said target molecule are selected for concatenation.

101. The method of claim 79 wherein a RNA molecule is selected as said target molecule.

102. The method of claim 101 wherein said RNA molecule is from about 10 to about 200 nucleotides in length.

103. The method of claim 102 wherein said RNA molecule is from about 15 to about 100 nucleotides in length.

104. The method of claim 102 wherein said RNA molecule comprises an isolated or purified portion of a larger RNA molecule.

105. The method of claim 101 wherein said RNA has secondary and ternary structure.

106. The method of claim 79 wherein said each of said fragments independently have a molecular mass of less than 400.

107. The method of claim 106 wherein said each of said fragments independently have a molecular mass of less than 200.

108. The method of claim 79 wherein said each of said fragments independently have no more than three rotatable bonds.

109. The method of claim 79 wherein said each of said fragments independently have no more than one sulfur, phosphorous or halogen atom.

110. The method of claim 101 wherein said RNA is an ammonium salt.

111. The method of claim 79 wherein said target molecule exposed to said ligand fragments is introduced into said

mass spectrometer via an electrospray ionization source.

112. The method of claim 111 wherein said electrospray ion source is a Z-spray, microspray, off-axis spray or pneumatically assisted electrospray.

113. The method of claim 79 wherein said electrospray ion source further includes countercurrent drying gas.

114. The method of claim 79 wherein said target molecule exposed to said ligand molecules is interrogated by an mass analyzer, a quadrupole, a quadrupole ion trap, a time-of-flight, a FT-ICR or a hybrid mass analyzer.

115. The method for refining the binding of a ligand to a target molecule comprising:

selecting a first virtual fragment of said ligand;

selecting a second virtual fragment of said ligand;

virtually concatenating said ligand fragments together to form an *in silico* 3D model of said concatenated ligand fragments;

positioning said *in silico* 3D model of said concatenated ligand fragments on an *in silico* 3D model of said target molecule;

scoring said positioning of said *in silico* 3D model of said concatenated ligand fragments on said *in silico* 3D model of said target molecule; and

refining said positioning of said *in silico* 3D model of said concatenated ligand fragments on said *in silico* 3D model of said target molecule using the results of said scoring.

116. The method of claim 115 wherein said scoring uses one or more hydrophobic, hydrogen-bonding and

electrostatic interactions between said *in silico* 3D model of said concatenated ligand fragments and said *in silico* 3D model of said target molecule.

117. The method of claim 115 further including;

procuring a real ligand corresponding to said first virtual ligand fragment;

procuring a real second ligand corresponding to said second virtual ligand fragment;

covalently joining said first and said second real ligand fragments together in a structural configuration that mimics said virtually concatenating said ligand fragments;

exposing said target molecular to said covalently joined ligand fragments; and

re-interrogating said target molecule exposed to said covalently joined ligand fragments in a mass spectrometer to identify binding of said covalently joined ligand fragments and said target molecule.

118. The method of claim 115 comprising:

modifying said first virtual ligand fragment by making a structural derivative of said virtual ligand fragment to form a modified first virtual ligand fragment;

virtually concatenating said modified first virtual ligand fragment and said second virtual ligand fragment together to form a modified *in silico* 3D model of said concatenated ligand fragments;

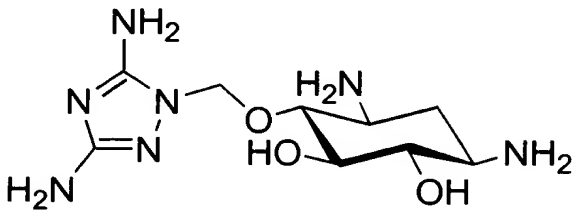
positioning said modified *in silico* 3D model of said concatenated ligand fragments on an *in silico* 3D model of said target molecule;

scoring said positioning of said modified *in silico* 3D model of said concatenated ligand fragments on said *in*

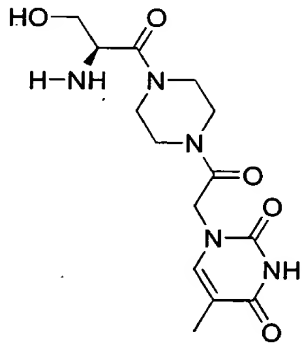
silico 3D model of said target molecule; and

refining said positioning of said modified *in silico* 3D model of said concatenated ligand fragments on said *in silico* 3D model of said target molecule using the results of said scoring..

119. A compound selected from the group consisting of:



and



120. The method according to claim 63, wherein the relative proximity of the first ligand binding site to the second ligand binding site is proportional to the length of the substituent group pending from a first ligand derivative that inhibits the binding of the second

ligand to the target substrate or has a competitive binding interaction with the second ligand for the target substrate.